REMARKS

Applicants want to thank the Examiner for the Interview conducted January 30, 2001. The Interview was very informative and productive.

Upon entry of the above amendment, claims 9 and 18-22 will be pending in the above-identified application. Applicants amended claims 9, 18 and 22 to clarify the language. Applicants have not raised any issue of new matter.

Applicants respectfully request the Examiner consider the above amendments and following remarks and enter them into the record. Applicants have not raised any issue to cause the Examiner to further search.

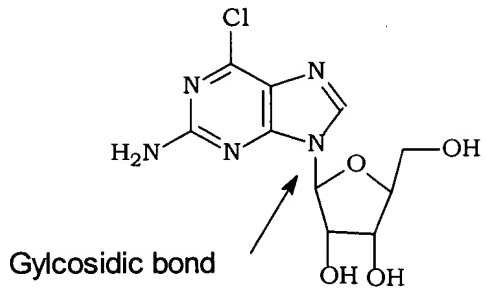
Issues under 35 U.S.C. §112

Claims 9, and 18-22 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants traverse this rejection. Applicants' item numbers correspond to the item numbers in the Office Action.

1. Glycosidic Bond

During the Interview of January 30, 2001, Applicants presented a Med-Line search of the term "glycosidic bond", with 32,000 hits. This evidences that the term is well used in the

art. In addition, Applicants explained the diagrams present in the Response filed March 10, 2001. The following diagram indicates a glycosidic bond.



The glycosidic bond is the bond between the aglycone and the glycoside in a nucleoside. More particularly in the above diagram, the nitrogen of the purine is bound to the anomeric carbon of ribose. These types of linkages are unstable under the conditions required for condensation of the amine with dichloropyrimidines.

The instability exists from a nitrogen atom bound to a carbon atom that is bound to an oxygen atom. This structure is an aminal and the aminal will "open up" in the harsh conditions of the reaction. The Examiner expressed concern in the Interview as to the definition of a sugar or carbohydrate. Applicants use the term "glycosidic bond" to describe or define the unstable aminal formation that generally is a part of a carbohydrate structure with an amine bonded to the anomeric carbon.

The Examiner requested a clearer explanation of the term "glycosidic bond" during the Interview. Applicants believe that the specification and the explanation above sufficiently describe the term such that a skilled artisan in organic synthesis would understand the term. "[A] patentee is free to be his own lexicographer." Hormone Research Foundation Inc. v. Genetech Inc., 904 .2d 1558, 15 U.S.P.Q.2d 1039 (Fed. Cir. 1990). "Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." MPEP §2173.05(b).

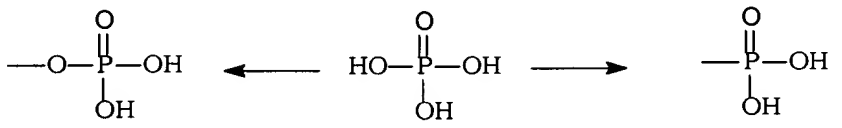
2. Acyclic Group

Applicants have amended claims 9, 18 and 22 to address the Examiner's concerns. The Examiner recited during the Interview that the additional limitations of substitutions by heteroatoms were redundant; thus, we have deleted such language, but assert that the claim has not been narrowed in any manner.

3. Phosphonyl

The Examiner is under the impression that group $-P(O)(OH)_2$ is a "phosphoryl" group, but during the Interview, the Examiner and Applicants failed to discover evidence of such an assumption. Applicants assert that the term "phosphonyl" is the correct term for the group $-P(O)(OH)_2$.

As discussed at the Interview, phosphoryl and phosphonyl are groups derived from phosphonic acid. Applicants assert that phosphonyl has three oxygens bound to phosphorus, and phosphoryl has four oxygen bound to phosphorus. See below.



Applicants assert that a skill artisan would understand the term "phosphonyl" in light of the specification and the general understanding of the art.

4. Heterocyclic

During the Interview, the Examiner stated that Applicants could amend the claims to identify the heteroatoms present. Applicants have amended the claims to identify the heteroatoms present.

5. C_{3-7} carbocyclic group

The Examiner has raised concerns that the term "group" is indefinite. The claim language reads "a C_{3-7} carbocyclic group, optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected

hydroxyl, azido, phosphonyl, and halogen." Applicants assert that a skilled artisan reading the above limitation in context would understand "C_{3-7} carbocyclic group" to be the cyclic group and the following substitutents to be substituted on the carbocyclic group.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejections.

ISSUE UNDER 35 U.S.C. § 103(a)

Claims 9, 18-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Daluge '697 (USP 5,087,697) in view of Vince '224 (USP 4,916,224) or Daluge '671 (USP 5,049, 671), further in view of Norbeck '703 (USP 4,988,703), Vince '607 (USP 5,736,607), Borthwick '531 (4,857,531) or Shealy '736 (USP 4,728,736). Applicants submit that patentable distinctions exist between the cited prior art and the present invention.

The Examiner has identified the significant difference between the primary reference Daluge '697 and the present invention in that the present invention does not have a protecting group on the 2-position amino group in the process of the purine synthesis. Applicants have explained in the March 10, 2000 Response that the prior art of record shows that a synthesis with an unprotected amine results in low yield "dark

red syrups" and low yield "sticky foams" and "red filtrates" that are unsuitable for large scale manufacturing of product. *See page 5, last paragraph of March 10, 2000 Response.*

Applicants have attached a 37 C.F.R. §1.132 Declaration from Dr. Susan M. Daluge. Dr. Daluge is an inventor of the present application and an inventor of Daluge '697. Dr. Daluge explains in the Rule 132 Declaration that not having the amino protecting group resulted in a difficult purification step due to side-reactions. The difficult reaction resulted in a reduced yield in the important step of purine formation. Furthermore, Dr. Daluge explains that the reactions without the amine protecting group resulted in tars, which are problemsome as intermediate products in a total synthesis.

The Rule 132 Declaration provides testimony that a skilled artisan would not be motivated to remove the amine protecting group at an earlier step in the total synthesis, because a skilled artisan would expect an unstable compound that would hamper purification and reduce overall yield of purine synthesis.

Daluge '697 has two steps to achieve the final purine product in Examples 27 and 28. Daluge '697 also has a one step process in Example 4. Daluge '697 sets forth in Examples 27 and 28, a cyclization step and a deprotection step, respectively. The cyclization step is a difficult reaction with a 53% yield

followed by an 80% yield of removing the 2-positon amino protecting group. In Example 4 of Daluge '697, the purine compound is collected in a 46% yield after a difficult column chromatography step. Thus, a skilled artisan would not have a reasonable expectation of success of using either of the Daluge '697 processes or combining them to make a purine product in high yield without a chromatography step.

In contrast, the present process gives a high yield without a chromatography step, which makes it desirable in a manufacturing process of a drug. In example 8, page 21 of the present invention, Applicants achieve a 92% yield of a purine product.

The Examiner must present a *prima facie* case of obviousness consisting of motivation or suggestion to modify or combine references such that one of ordinary skill in the art has a reasonable expectation of success of using the present process. "Obviousness can only be established by combining or modifying the teaching of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP 2143.01, *citing* In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). The cited references fail to suggest a process as set forth in the present claims. Because the products and yield

disclosed in the prior art are significantly inferior to the present invention, the present invention is patentable over the cited prior art.

Therefore, patentable distinctions exist between the present invention and the cited reference. Applicants respectfully request withdrawal the 35 U.S.C. § 103(a) rejection.

ISSUE UNDER 35 U.S.C. § 103(a)

Claims 9, 18-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over EP '544 (EP 413,544) in view of Norbeck '703, Vince '607, Borthwick '531 or Shealy '736. Applicants submit that patentable distinctions exist between the cited prior art and the present invention.

Applicants have amended claim 9 to remove protected hydroxyls from the definition of variable R^3. Applicants assert that the compounds of EP '544 are outside the scope of the present invention, because $O(CH_2)_3OR_5$ fails to fall within the definition of R^3.

EP '544 fails to disclose or suggest the process of the present invention, because it discloses a fundamentally different process using different reactants and different compounds. EP '544 fails to provide motivation for any other

substitutions at the R^3 variable position; thus, a *prima facie* case of obviousness has not been presented.

Therefore, significant patentable distinctions exist between the present invention and the cited reference. Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

ISSUE UNDER 35 U.S.C. § 103(a)

Claims 9, 18-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Norbeck '703, Vince '607, Borthwick '531 or Shealy '736 in view of EP '544 or Daluge '697. Applicants submit that patentable distinctions exist between the cited prior art and the present invention.

Applicants have presented arguments and evidence that the cited references above fail to suggest the present invention. EP '544 fails to disclose the compounds present in the present invention, and Daluge '697 fails to provide motivation to remove the amine protecting group to obtain good yields without side-reactions. The combined references fail to provide a cohesive idea that results in the present invention.

Applicants have presented, on the record in previous Responses, the state of the art. The attached Rule 132 Declaration provides evidence that a skilled artisan would not

expect success with removing the amino protecting group from the total synthesis of the purine product. "[T]herefore an examiner may often find every element of the claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'" In re Roufett, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998), *quoting* Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996). Applicants assert that a skilled artisan would not have been motivated to combine the cited prior art as assumed by the Examiner, because the expected results would be poor.

Therefore, patentable distinctions exist between the present invention and the cited reference. Applicants respectfully request the Examiner to withdraw the 35 U.S.C. § 103(a) rejection.

Conclusion

Applicants submit for the reasons stated above that the present claims define patentable subject matter such that this application should be placed into condition for allowance.

If the Examiner has any questions regarding the above matters, please contact Applicants' representative, Mark W. Milstead (Reg. No. 45,825), in the Washington, metropolitan area at the telephone number listed below.

Pursuant to 37 C.F.R. 1.17 and 1.136(a), the Applicants respectfully petition for a two (2) month extension of time for filing a response in connection with the present application. The required extension fee of $390.00 is attached hereto.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By: _____

Gerald M. Murphy, Jr.
Reg. No.: 28,977

P. O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/MWM/gml

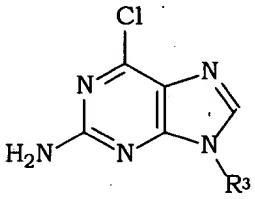
Attachment: Version with Marking to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

The claims have been amended as follows.

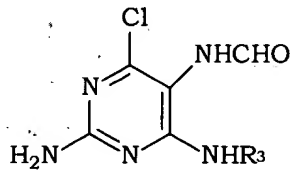
9. (Five Times Amended) A process for the preparation of a compound of formula (VII)



(VII)

wherein R^3 is hydrogen; hydroxyl [or protected hydroxyl]; a C_{3-7} carbocyclic group, optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and [or] halogen; an acyclic group, [wherein carbon atoms may be substituted by one or more heteroatoms selected from N, O and S, and] wherein such acyclic groups may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and [or] halogen; or a C_{4-7} heterocyclic group, wherein [at least one carbon atom is replaced by] said C_{4-7} heterocyclic group has a one or more heteroatoms selected from the group consisting of a N, O [or] and S atom and wherein such

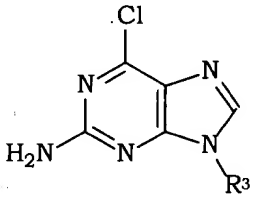
C_{4-7} heterocyclic group may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and [or] halogen; provided that such groups are not attached by a glycosidic bond, comprising reacting a compound of formula (VI)



(VI)

wherein R^3 is as defined above, with a trialkylorthoformate in the presence of an aqueous acid.

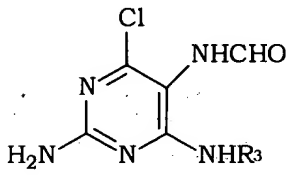
18. (Amended Five Times) A process for the preparation of a compound of formula (VII)



(VII)

wherein R^3 is a C_{3-7} carbocyclic group, optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and [or] halogen; an acyclic group, [wherein carbon atoms may be substituted by one or more heteroatoms selected

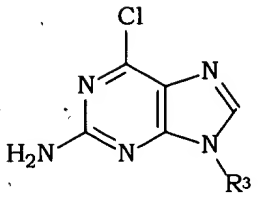
from N, O and S, and] wherein such acyclic group may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and [or] halogen; or a C_{4-7} heterocyclic group, wherein [at least one carbon atom is replaced by] said C_{4-7} heterocyclic group has a one or more heteroatoms selected from the group consisting of a N, O [or] and S atom and wherein such C_{4-7} heterocyclic group may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and [or] halogen; provided that such groups are not attached by a glycosidic bond, comprising reacting a compound of formula (VI)



(VI)

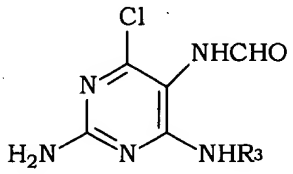
wherein R^3 is as defined above, with a trialkylorthoformate in the presence of an aqueous acid.

22. (Twice Amended) A process for the preparation of a compound of formula (VII)



(VII)

wherein R^3 is an acyclic group, [wherein carbon atoms may be substituted by one or more heteroatoms selected from N, O and S, and] wherein such acyclic group may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and [or] halogen; provided that such groups are not attached by a glycosidic bond, comprising reacting a compound of formula (VI)



(VI)

wherein R^3 is as defined above, with a trialkylorthoformate in the presence of an aqueous acid.